Remarks

Claims 1-10, 12, 14-18, 20-28 and 30-41 are pending in the present application. The following objections and rejections are at issue and are set forth by number in the order in which they are addressed:

1. The specification is objected to for use of trademarks;
2. The drawings are objected to as duplicative;
3. The claims are rejected for double patenting;
4. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;
5. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter;
6. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al.;
7. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Burns et al.;
8. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Schroder et al.;
9. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Primus and Kolb et al.;
10. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Naldini et al.

Claims 1 and 21 have been amended in order to further Applicant's business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business

Goals (PBG; 65 Fed. Reg. 54603 (September 8, 2000), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. None of the claim amendments made herein are intended to narrow the scope of any of the amended claims within the meaning of *Festo Corp. v. Shokestu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) or related cases.

1. The specification has been amended.

The specification has been amended to correct any issues with respect to use of trademarks.

2. The drawings are proper.

The Examiner has objected to the drawings because they allegedly do not comply 37 CFR 158(a) and 37 CFR 1.83. Applicants respectfully traverse. 37 USC 1.58(a) provides:

The specification, including the claims, may contain chemical and mathematical formulae, but shall not contain drawings or flow diagrams. The description portion of the specification may contain tables, but the same tables may only be included in both the drawings and description portion of the specification if the application was filed under 35 U.S.C. 371. Claims may contain tables either if necessary to conform to 35 U.S.C. 112 or if otherwise found to be desirable.

This section states that if the description contains tables, those tables may not be included in the drawings. This section does not state, as argued by the examiner, that sequences included in a sequence identification listing may not be included in the drawings.

37 USC 1.83(a) provides that:

The drawing in a nonprovisional application must show every feature of the invention specified in the claims. However, conventional features disclosed in the description and claims, where their detailed illustration is not essential for a proper understanding of the invention, should be illustrated in the drawing in the form of a graphical drawing symbol or a labeled representation (e.g., a labeled rectangular box). In addition, tables and sequence listings that are included in the specification are, except for applications filed under 35 U.S.C. 371, not permitted to be included in

the drawings.

This provision states that sequence listings included in the specification are not permitted to be included in the drawings. Applicants respectfully note that the instant drawings are not sequence listings. In other words, the drawings are not identical to the sequence listing portion of the specification. Instead, the drawings include information on the subparts of the vector sequences. This is not a case where the sequence listing has been included in a drawing. Accordingly, Applicants request that this objection be withdrawn.

3. Double patenting.

A terminal disclaimer will be filed upon resolution of the remaining rejections.

4. The claims are definite.

Claims 1 and 21 have been amended to refer to a method of producing a protein in the preamble and a secretion signal sequence, respectively. Applicant's believe these amendments renders the rejections moot.

5. The claims do not contain new matter.

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. Applicants addressed this rejection in their previous response, however, the Examiner has not addressed the arguments contained therein. For convenience, those arguments are repeated here.

The specification clearly establishes that the Applicants contemplate any number of integrations within the ranges specified. As provided in the Specification, page 3:25-26: "In some embodiments, the genome comprises at least 5, and preferably, at least 100 integrated integrating vectors." As can be seen, the claimed range of 20 to 100 integrated vectors is clearly within the described range of 5 to 100 integrated vectors per cells.

Applicants further note that the subject matter of claim need not be described literally or "in ipsis verbis" in order for the specification to satisfy the written description requirement. See, e.g., In re Lukach, 442 F.2d 967, 969, 169 USPQ 795, 796 (C.C.P.A. 1971). It is clear that the claimed lower limit of 20 integrations per cell is within the ranges taught in the specification.

Thus, support for the claim limitations exists and the claims limitations are new matter. In this regard, the limitations are similar to those addressed by the CCPA in In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). There, the specification described a step of a process as achieving a solids concentration of a coffee extract of 25-60% and gave specific examples of 36% and 50%. The claims at issue specified a solids concentration of between 35% and 60%. The CCPA overturned the rejection of this claim, finding that the narrowed range was within the range taught in the patent specification. Id. at 264, 191 USPQ at 98. In the instant case, the range of 20-100 integrations per cell is clearly within the ranges taught in the specification. There is no new matter.

As such, the claim limitation of 20 to 100 integrated vectors per cell is supported by the specification. Applicants respectfully request that this ground of rejection be withdrawn.

6. The claims are not obvious over Mathor, Felts and Inaba.

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al. Applicants respectfully traverse.

The Examiner admits at page 14 of the Office Action that Mathor does not "specifically teach a genome comprising from about 20 to about 100 integrated vectors (claims 1 and 41), a multiplicity of infection from about 10 to 1000 (claim 1), or clones expressing 10, or 50 pg of protein per cell per day (claims 32-34)." The Examiner then goes on to argue that Felts teaches that the advantage of retroviral vectors s that copy number can be easily controlled by varying MOI and thus "it would have been obvious to one of skill in the art, at the time the invention was made, to use different MOIs to achieve the claimed ranges of integration events, with a reasonable expectation of success. The motivation to do so is provided by Mathor et al. who teach the importance of specifying the level of transgene expression for gene therapy." Office Action at 7. The Examiner further recognizes that Mathor et al. does not teach serial transduction of host cells, but then argues that Inaba teaches serial transduction over a 10-14 day period. The Examiner argues that there is motivation to modify Mathor because Inaba teaches that serial transduction results in higher transduction rates. Office Action at 15.

A *prima facie* case of obviousness requires the Examiner to cite a combination of references which (a) disclose the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of the these three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitles Applicant to allowance of the claims in issue.[1] In addressing this rejection, Applicants focus on the independent claims since non-obviousness of an independent claim necessarily leads to non-obviousness of claims dependent therefrom.[2]

First, the Examiner admits that Mathor does not teach the claimed limitation of 20 to 100 integrations. The other cited references do not cure this defect. Neither Coffin nor Inaba teach cells containing from 20 to 100 integrants. The references do not suggest this limitation either. In fact, the Examiner can pint to no explicit or implicit statements in the references that suggest cells containing from 20-100 integrants. Even though the Examiner argues that it would be obvious to use different MOIs to achieve the claimed ranges, there is no suggestion in the references to make cells with the claimed ranges. That is what is required. AS prima facie case of obviousness has not been established because the references do not teach or suggest all of the claim limitations.

Second, the Federal Circuit has held that when determining is there is a suggestion to modify or combine references, "the full field of the invention must be considered for the person of ordinary skill is charged with knowledge of the entire body of technical literature, including that which may lead away from the claimed invention." In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). Applicants initially note that none of the references cited by the Examiner teach the claimed range of vector integrations. Thus, the Examiner has attempted to modify the primary cited reference to provide the claimed integration ranges.

Applicants respectfully submit that a person of skill in the art would not combine or modify the references to provide the claimed integration ranges. The full field of the invention must be considered. Coffin et al., Development and Applications of Retroviral Vectors, Chapter

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1 *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

2 §MPEP 2143.03.

9 in Retroviruses, 1997, p. 437-473, which was cited by the previous Examiner on Form PTO-829 mailed November 17, 2005, teaches at page 463, column 1 that: "Insertional mutagenesis by retroviral vectors is often cited as a safety concern. This issue has been raised because proviral insertion can cause the inactivation of tumor suppressor genes or the activation of oncogenes." Applicants respectfully submit that references such as Arai et al., Virology 260:109-115 (1999), which was cited by the previous Examiner on Form PTO-829 mailed November 17, 2005, specifically teach away from the current claims. Arai et al. state:

> When a 3Y1 was transduced with the pseudotyped vector at an m.o.i. of 100, a significant proportion of the cell population became detached from the plate within two days. Since apoptotic cells were detected from among these cells at 1 day after transduction by means of the TUNEL method (data not shown), proviral integration with a very high copy number seems to cause cell death. While we did not address the reason for this induction of apoptosis, a major factor could be that the multiple integration causes insertional mutagenesis in essential genes. The toxicity of overproduced LacZ was not the major reason, because LacZ activity observed in 3Y1 transduced at m.o.i. 100 at 1 day after the transduction was less than that detected in 3Y1 transduced at m.o.i. 30 at 3 days after the transduction, and the latter cells showed only marginal signs of apoptosis (data not shown).

Thus, Arai teaches that "proviral integration with a very high copy number seems to cause cell death." Upon reading reading Arai, one of skill in the art would be "discouraged" from using a the claimed multiplicity of infection and copy insert number to obtain cells for the production of a secreted protein.

References such as these lead away from the claimed invention. A person of skill in the art, knowing of these references, would not be motivated to use different MOIs to achieve the claimed number of integrations because the prior art teaches that high levels of integrations are undesirable. Moreover, one of skill in the art would not be motivated to increase gene expression by increasing the number of integrations because the prior art teaches that high numbers of integrations are undesirable. None of the references cited by the examiner teach or suggest the desirability of the claimed range of integrations.

Indeed, Applicants respectfully submit that the Examiner is applying hindsight. When applying 35 U.S.C. §103, the references must be considered as whole and must suggest the desirability and thus the obviousness of making the combination.[3] The purpose behind this requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent decision, articulates this position:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.[4]

Here, the problem confronted by the Inventors was the need for increased protein production from host cells. The Inventors solved this problem by creating cell lines with multiple integrated vectors. A person of skill in the art would not have been motivated to select elements from the cited prior art references in the manner suggested by the Examiner because those of skill in the art would have known that high numbers of integration are undesirable.

Applicants respectfully submit that this ground of rejection should be withdrawn.

7. The claims are not obvious over Mathor, Felts, Inaba and Burns.

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Burns et al. This combination of references (i.e., the addition of Burns et al.) does not cure the deficiencies noted for the combination of Mathor, Felts, and Inaba. Burns et al., alone or in combination with the other three cited references, does not teach or suggest the claimed range of 20-100 integrants as explained in Section 4 above. Applicants respectfully request that this ground of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

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3 *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n. 5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986).

4 *See In re Rouffet et al.*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998).

8. The claims are not obvious over Mathor, Felts, Inaba and Schroder

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Schroder et al. This combination of references (i.e., the addition of Schroder et al.) does not cure the deficiencies noted for the combination of Mathor, Felts, and Inaba. Schroder et al., alone or in combination with the other three cited references, does not teach or suggest the claimed range of 20-100 integrants as explained in Section 4 above. Applicants respectfully request that this ground of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

9. The claims are not obvious over Mathor, Felts, Inaba, Primus and Kolb

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Primus and Kolb et al.. This combination of references (i.e., the addition of Primus and Kolb et al.) does not cure the deficiencies noted for the combination of Mathor, Felts, and Inaba. Niether Primus nor Kolb, alone or in combination with the other three cited references, teach or suggest the claimed range of 20-100 integrants as explained in Section 4 above. Applicants respectfully request that this ground of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

10. The claims are not obvious over Mathor, Felts, Inaba and Naldini

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Naldini et al. This combination of references (i.e., the addition of Naldini et al.) does not cure the deficiencies noted for the combination of Mathor, Felts, and Inaba. Naldini et al., alone or in combination with the other three cited references, does not teach or suggest the claimed range of 20-100 integrants as explained in Section 4 above. Applicants respectfully request that this ground of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

CONCLUSION

All grounds of rejection and objection of the Office Action of October 26, 2006 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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